UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/618,129	07/17/2000	Xiao Bing Wang	TRIM1	8510

24504 7590 03/05/2004

THOMAS, KAYDEN, HORSTEMEYER & RISLEY, LLP
100 GALLERIA PARKWAY, NW
STE 1750
ATLANTA, GA 30339-5948

EXAMINER	
SPIEGLER, ALEXANDER H	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/618,129	WANG, XIAO BING	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5,8,9,11-37 and 39-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5,8,9,11-37 and 39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/28/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 26, 2003 has been entered.

Status of the Application

2. Currently, claims 2-3, 5, 8-9, 11-37 and 39-41 are pending and are rejected herein.

Information Disclosure Statement

3. The information disclosure statement filed on May 28, 2003 complies with CFR 1.97, 1.98, and M.P.E.P. 609, and has been considered (see enclosed signed PTO-1449).

Specification

4. The disclosure is objected to because of the following informalities:

A) The use of trademarks have been noted in this application. (See, for example, pages 19 "QIAGEN", "PERKIN ELMER", page 20, "PROMEGA", "INVITROGEN", etc.). These should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

B) Claim 15 recites, "on or more", which should recite, "one or more".

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2-3, 5, 8-9 and 11-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 2-3, 5, 8-9 and 11-37 over "the variant target nucleotide base" because this recitation lacks antecedent basis.

B) Claim 13 over "the 'Klenow fragment' thereof" because this recitation lacks antecedent basis.

C) Claims 28, 32, 34 and 36 over "extragenomic" because it is not clear as to what this recitation means, there is no definition of this term in the specification, and it is not an art recognized term. Accordingly, "extragenomic" is indefinite.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 2-3, 5, 8-9, 11-37 and 39-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Soderlund (US 6,013,431).

Regarding Claims 2-3, 5, 37 and 39-41, Soderland teaches a method for detecting the presence of a nucleic acid of interest having a variant of a known nucleotide base in a predetermined position of a known nucleic acid comprising:

(a) obtaining a nucleic acid of interest having a target nucleotide base at the predetermined position in a template of the nucleic acid of interest;

(b) preparing an unlabeled primer complementary to a sequence immediately upstream of the target nucleotide base;

(c) treating a sample containing the nucleic acid of interest, if the nucleic acid is double-stranded, so as to obtain unpaired nucleotide bases spanning the predetermined position, or directly employing step (d) if the nucleic acid of interest is single-stranded;

(d) annealing the primer from (b) with the nucleic acid of interest from (c) to obtain a primer-nucleic acid duplex, wherein the target nucleotide base in the nucleic acid of interest is the first unpaired base immediately downstream of the 3' end of the primer;

(e) mixing the primer-nucleic acid duplex from (d) with a primer extension reaction reagent comprising: (i) three types of non-terminator nucleotides that are not complementarily matched to the known nucleotide base in the predetermined position of the nucleic acid of interest, wherein at least one type of the non-terminator nucleotide is labeled with a detectable marker; and optionally (ii) one type of terminator nucleotide that is complementarily matched to the known nucleotide base in the predetermined

position of the nucleic acid of interest, wherein the terminator nucleotide is not labeled;

(f) extending the primer extension reaction by enzymatic or chemical means to form a labeled primer extension product comprising a plurality of labeled non-terminator nucleotides, wherein a labeled primer extension product does not form when the target nucleotide base in the predetermined position of the nucleic acid of interest is the same as the known target nucleotide base in the predetermined position of the known nucleic acid; and

(g) determining the presence of the nucleic acid of interest having the variant target nucleotide base at the predetermined position in the nucleic acid of interest by detecting the presence of the labeled primer extension product, wherein detecting the labeled primer extension product is not based on size.

(See col. 3, lines 34-58; col. 4, lines 59-63; cols. 7-8, Examples 1-7, and col. 18, ln. 19-53, for example).

With respect to the recitations of "variant" and "known", there are no specific definitions of these recitations in the specification, and accordingly, they have been given the broadest reasonable interpretation consistent with the supporting disclosure and those skilled in the art. See MPEP 2111. Specifically, the specification states:

> By "standard nucleotide base", it includes *any known base, which may include wild-type or a known mutant base so long as the base is known and it is desired to know its variant.* Thus, as an example, normal base can be a known wild-type base for which a mutation is sought at the position. Inversely, the known base can be a known mutant for which the presence of a wild-type base is sought at the position. Alternatively, the known normal base can be a known mutant for which another mutant variant base is sought. Therefore, *the method of the invention can be applied to any known sequence that can be used to determine the presence of any other base variant at the site.*

(emphasis added) (page 10-11).

Accordingly, the instant invention is drawn to detecting variations of "known" bases,

wherein the known base *may* be either a "wild-type" or "mutant" base. Soderlund teaches "a method to determine *a* specific nucleotide *variation in a previously defined region*" (col. 4, lines. 59-60). Thus, Soderlund teaches detecting variations of "known" bases, since Soderlund teaches detecting variations from "previously defined regions". A "previously defined region" (e.g., a previously defined base) is interpreted as a "known" base.

The claims are drawn to detecting the presence of the nucleic acid of interest having the variant target nucleotide base at the predetermined position in the nucleic acid of interest by detecting the presence of the labeled primer extension product. That is, the claims are drawn to detecting a variant of a "known" base by detecting the presence of a labeled extension product. Thus, a labeled primer extension product could be formed by the incorporation of a labeled dNTP, wherein the dNTP corresponds to a variant of a "known" base. Soderlund teaches this detection of a labeled primer extension product, which is indicative of a variant of a "known" base (see, for example, col. 8, lines 49-52).

Regarding Claim 8, Soderlund teaches that two or more differently labeled dNTPs (non-terminator nucleotides) can be added to the primer-nucleic acid duplex, wherein the detection is better interpreted by adding dNTPs that are different than the terminator nucleotide (See col. 8, ln. 58-64, for example).

Regarding Claim 9, Soderlund teaches the use of this invention with various labels such as radioactive or fluorescent labels (see examples 1-7, col. 9-18, for example).

Regarding Claims 11-14, Soderlund teaches that the primer extension reaction can be performed by enzymatic means using template dependent enzymes (i.e. T7 DNA polymerase, T4 DNA polymerase, reverse transcriptase, etc.) (col. 8, ln. 10-17, for example).

Regarding claims 15-22, Soderlund teaches that the primer may contain an attachment moiety (i.e. biotin, antigens, etc.) (See col. 6, ln. 16-31, for example), that permits affinity separation of the primer from the unincorporated reagent and/or the nucleic acid of interest (col. 6, ln. 53 to col. 7, ln. 26, for example), and furthermore, that a solid support may be used in the separation process (col. 6-7, for example).

Regarding Claims 23-36, Soderlund teaches the source of the target nucleic acid of interest can be any form of RNA or DNA obtained via amplification (for example), from any source such as from a human, animal, plant, or microbe (See cols. 1-5 and Examples 1-7).

Applicant's Arguments

Applicant argues:

1) Soderlund is directed to a sequencing method, whereas the instant method is not a sequencing method.

2) Soderlund fails to teach a reaction mixture having three types of non-terminator nucleotides that are not complementarily matched to the known nucleotide base. Soderlund teaches "using a primer extension reaction mixture containing a labeled known nucleotide so that the detection of a labeled primer extension product means that target nucleotide at the predetermined position is complementary to the labeled known nucleotide". See Applicant's arguments.

3) Soderlund fails to disclose using unlabeled ddNTPs that are complementary to a known nucleotide at a predetermined position so that labeled primer extension products will only form when there is a variation at the predetermined position.

4) Soderlund fails to disclose a primer extension reaction is not formed because Soderlund is directed to determining the identity of the nucleotide at the predetermined position.

Response to Applicants Arguments

Applicant's arguments have been considered, but are not persuasive for the following reasons:

1) Both the instant claims and the teachings of Soderlund are drawn to methods of detecting variations of "known" nucleotide bases. Specifically, for example, Claim 37 is drawn to *detecting the presence of a nucleic acid interest having a variant of a known nucleotide base* in a predetermined position of a known nucleic acid. Soderlund teaches this detection of a variant of a "known" base (see, for example, col. 8, lines 49-52).

2) Soderlund does teach the use of three non-terminator nucleotides that are not complementary to the known nucleotide base. See, for example, col. 8, lines 49-52 and lines 58-60. Specifically, the non-terminator nucleotides correspond to a variant of a "known" nucleotide. Applicant's argument with respect to Soderlund's reaction mixture containing a labeled "known" nucleotide is somewhat confusing, since Soderlund is adding a labeled non-terminator (e.g., a labeled dNTP), which is the same type of labeled non-terminator as in the instant invention (e.g., a labeled dNTP, see claim 5). That is, it is assumed that all dNTPs are "known" in the sense that they are dATPs, dTTPs, dGTPs, dCTPs or dUTPs.

3) Applicant is arguing limitations not required by the claims, since the claims do not require the use of an unlabeled ddNTPs. At most, Claims 37 and 41 suggest that the use of terminators (e.g., ddNTPs) is "optional", and Claims 39 and 40 do not mention ddNTPs at all. It is also noted the use of term "known" is relative and is not defined in the specification.

Furthermore, as required by the claims, Soderlund teaches the detection of a labeled extension product, wherein the presence of the extension product is indicative of the presence of a variant of a "known" nucleotide base.

4) Like the instant invention, Soderlund's labeled primer extension product will not form if the target nucleotide base in the predetermined position is the same as the known target nucleotide base. For example, Soderlund teaches a labeled extension product when there is a variation of a "known" nucleotide base, and therefore, there will not be a labeled extension product if the target nucleotide base in the predetermined position is the same as the "known" target nucleotide base.

For these reasons, and those of record, the rejection is maintained.

9. Claims 2-9, 11-15, 17, 23-37 and 39-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Fahy et al. (WO 96/30545, previously cited).

Regarding Claims 2-3, 5, 37 and 39-41, Fahy teaches a method for detecting the presence of a nucleic acid of interest having a variant of a known nucleotide base in a predetermined position of a known nucleic acid comprising:

(a) obtaining a nucleic acid of interest having a target nucleotide base at the predetermined position in a template of the nucleic acid of interest;

(b) preparing an unlabeled primer complementary to a sequence immediately upstream of the target nucleotide base;

(c) treating a sample containing the nucleic acid of interest, if the nucleic acid is double-stranded, so as to obtain unpaired nucleotide bases spanning the predetermined position, or directly employing step (d) if the nucleic acid of interest is single-stranded;

(d) annealing the primer from (b) with the nucleic acid of interest from (c) to obtain a primer-nucleic acid duplex, wherein the target nucleotide base in the nucleic acid of interest is the first unpaired base immediately downstream of the 3' end of the primer;

(e) mixing the primer-nucleic acid duplex from (d) with a primer extension reaction reagent comprising: (i) three types of non-terminator nucleotides that are not complementarily matched to the known nucleotide base in the predetermined position of the nucleic acid of interest, wherein at least one type of the non-terminator nucleotide is labeled with a detectable marker; and optionally (ii) one type of terminator nucleotide that is complementarily matched to the known nucleotide base in the predetermined position of the nucleic acid of interest, wherein the terminator nucleotide is not labeled;

(f) extending the primer extension reaction by enzymatic or chemical means to form a labeled primer extension product comprising a plurality of labeled non-terminator nucleotides, wherein a labeled primer extension product does not form when the target nucleotide base in the predetermined position of the nucleic acid of interest is the same as the known target nucleotide base in the predetermined position of the known nucleic acid; and

(g) determining the presence of the nucleic acid of interest having the variant target nucleotide base at the predetermined position in the nucleic acid of interest by detecting the presence of the labeled primer extension product, wherein detecting the labeled primer extension product is not based on size.

(See page 6, lines 31-36, pages 7-8, page 16, lines 17-37, pages 18-19, page 21, lines 27-32, for example).

With respect to the recitations of "variant" and "known", there are no specific definitions of these recitations in the specification, and accordingly, they have been given the broadest reasonable interpretation consistent with the supporting disclosure and those skilled in the art. See MPEP 2111. Specifically, the specification states:

> By "standard nucleotide base", it includes *any known base, which may include wild-type or a known mutant base so long as the base is known and it is desired to know its variant.* Thus, as an example, normal base can be a known wild-type base for which a mutation is sought at the position. Inversely, the known base can be a known mutant for which the presence of a wild-type base is sought at the position. Alternatively, the known normal base can be a known mutant for which another mutant variant base is sought. Therefore, *the method of the invention can be applied to any known sequence that can be used to determine the presence of any other base variant at the site.*

(emphasis added) (page 10-11).

Accordingly, the instant invention is drawn to detecting variations of "known" bases, wherein the known base *may* be either a "wild-type" or "mutant" base. Fahy teaches the dNTPs are not complementary to a "known" target nucleotide base (see page 19, lines 1-17; see also page 16, lines 17-20 and page 21, lines 27-32).

It is noted that, the terms "wild-type" and "mutant" are relative terms, which can be population specific. That is, these terms are not fixed terms; in one population a specific nucleotide may be considered "wild-type", but in a different population the specific nucleotide may be considered "mutant".

It is also noted that Fahy teaches the use of labeled dNTPs for detection of extension products (which is identical to the instant invention), and therefore, the detection the labeled primer extension product is not based on size, but on whether or not the product contains the label. See, for example, page 21, lines 27-32.

Regarding Claim 8, Fahy teaches the labeled dNTPs (non-terminator nucleotides) are labeled with the same or different detectable markers (See page 21, lines 15-23 and 27-32, for example).

Regarding Claim 9, Fahy teaches the use of this invention with various labels such as radioactive or fluorescent labels (See pages 15-16 and page 21, lines 15-23, for example).

Regarding Claims 11-14, Fahy teaches that the primer extension reaction can be performed by enzymatic means using template dependent enzymes (i.e., T7 DNA polymerase, Klenow fragment, reverse transcriptase, etc.) (See pages 19-20, for example).

Regarding claims 15 and 17, Fahy teaches that the primer may contain biotin (See page 21, lines 15-26, for example).

Regarding Claims 23-36, Fahy teaches the source of the target nucleic acid of interest can be any form of RNA or DNA obtained via amplification (for example), from any source such as from a human, animal, or microbe (See pages 9, 13-15, 17 and 58, for example).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 16 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fahy et al. (WO 96/30545, previously cited), as applied to claims 2-9, 11-15, 17, 23-37 and 39-41 above, and further in view of Soderlund (US 6,013,431).

The teachings of Fahy are presented above. Specifically, Fahy teaches the method of detection using a primer labeled with biotin. Fahy does not teach the primer permits affinity separation of the primer from the unincorporated reagent and/or the nucleic acid of interest or that a solid support may be used in the separation process.

However, Soderlund teaches a detection method wherein the primer may contain an attachment moiety (i.e. biotin, antigens, etc.) (See col. 6, ln. 16-31, for example), that permits affinity separation of the primer from the unincorporated reagent and/or the nucleic acid of interest (col. 6, ln. 53 to col. 7, ln. 26, for example), and furthermore, that a solid support may be used in the separation process (col. 6-7, for example). Soderlund teaches using attachment moieties (which can be used for linkage to a solid support) is advantageous in aiding the detection process by determining which strand the variable nucleotide occurs (col. 6, lines 7-9), purifying the reaction to ensure only bound material is analyzed (col. 6, lines 55-63), and making it possible to reuse the target nucleic acid if multiple determinations are to be performed on the same target sequence of interest (col. 6, lines 63-67).

Accordingly, in view of the teachings of Soderlund, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Fahy

so as to have used a primer comprising an attachment moiety which permits affinity separation of the primer from the unincorporated reagent and/or the nucleic acid of interest and to have used a solid support in the separation process. One of ordinary skill in the art would have been motivated to modify the method of Fahy in order to have achieved the benefit of aiding the detection process by determining which strand the variable nucleotide occurs, purifying the reaction to ensure only bound material is analyzed, and making it possible to reuse the target nucleic acid if multiple determinations are to be performed on the same target sequence of interest.

Conclusion

13. No claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (571) 272-0747. If attempts to reach Carla Myers are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alexander H. Spiegler
March 3, 2004

Carla Myers 313104
CARLA J. MYERS
PRIMARY EXAMINER